# **Cobalt-Catalyzed N-Alkylation of Amines with Alcohols**

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## **S** Supporting Information

ABSTRACT: A well-defined nonprecious metal cobalt(II) catalyst based on a pincer PNP ligand has been employed for the efficient N-alkylation of both aromatic and aliphatic amines with alcohols. A subtle change of reaction conditions (simply adding 4 Å molecular sieves) was observed to readily switch the resulting products (amines vs imines) with high chemoselectivity. A range of alcohols and amines including both aromatic and aliphatic substrates were efficiently converted to secondary amines in good-to-excellent yields when 2 mol % cobalt catalyst was used. Additional experiments indicate that a hydrogen-borrowing mechanism is responsible for the tandem acceptorless dehydrogenation/condensation/hydrogenation process.

P recious metal (Ru, Ir, Pd, etc.) catalysis has been involved in most crucial organic travel most crucial organic transformations to date, including some C-C and C-N bond-forming reactions.<sup>1</sup> High catalytic activity and turnover frequencies have been achieved by using such precious metal catalysts.<sup>1</sup> However, the scarcity, cost, and toxicity of precious metals can be problematic, making them less attractive for widespread and large-scale commercial applications in industry. In recent decades, the replacement of precious metal catalysts with earth-abundant element alternatives has become a focused research theme, in consideration of "greener" and more sustainable chemistry for the future.<sup>2</sup> Significant progress has been made in the development of homogeneous base metal (Fe, Co, Ni, etc.) catalysts,<sup>3,4</sup> although major challenges remain as the first-row transition metals tend to undergo one-electron changes in oxidation state and radical reactions, which has limited their applications as catalysts.

The catalytic N-alkylation of amines with alcohols provides a green and atom-economic pathway for the synthesis of substituted amines that have important synthetic applications in pharmaceutical chemistry.<sup>5-7</sup> Precious metal Ir- and Rucatalyzed amine alkylation by alcohols has been previously reported by several groups.<sup>8-10</sup> In these examples, a "hydrogenborrowing" mechanism has been proposed that involves three successive steps, i.e., acceptorless dehydrogenation of alcohols, imine formation, and the hydrogenation of imines using the hydrogen equivalents generated from the previous dehydrogenation step.<sup>11</sup> Despite such advances, well-defined molecular catalysts composed of earth-abundant metals for direct amine alkylation remain extremely scarce to date.<sup>12-14</sup> The only homogeneous catalyst system involving a Co<sup>II</sup> complex that catalyzed N-alkylation of aromatic amines by alcohols was reported very recently but required the use of a strong base



(potassium *tert*-butoxide).<sup>14</sup> Therefore, the discovery of new molecular catalysts based on nonprecious metals enabling this type of reaction is still highly desirable.

Recently, we have observed that an ionic cobalt(II) alkyl complex  $[(PNHP^{Cy})Co(CH_2SiMe_3)][BAr_4^F]$  (2, Scheme 1) built on a pincer-type PNP ligand carries out hydrogenation reactions as a precatalyst under mild conditions and at low H<sub>2</sub> pressure (1-4 atm).<sup>15–18</sup> The catalyst was found to be versatile for the highly efficient reduction of a broad range of chemicals including alkenes, aldehydes, ketones, and imines<sup>15,16</sup> and the transfer hydrogenation of a variety of polar double bonds, indicating great potential of cobalt in replacing precious metal hydrogenation catalysts.<sup>17</sup> Furthermore, it was revealed that the same cobalt complex catalyzed the acceptorless dehydrogenation of alcohols as well as the formation of imines from alcohols and amines upon heating a toluene solution of both substrates in the presence of in situ formed catalyst 2 (Scheme 2).<sup>18</sup> The capability of cobalt 2 in catalyzing acceptorless dehydrogenation has been further established by the Jones group very recently.<sup>19</sup> During the course of cobalt-catalyzed imine formation from alcohols and amines, we noticed that in a few cases reduced imines (amines) were formed as byproducts in less than 10% yield. We envisaged that a hydrogenation process of imine in the same catalytic system should have occurred and that it might be possible to switch the major products from imines to amines by altering the reaction conditions. Indeed, after many attempts, we were pleased to find that by simply adding 4 Å molecular sieves (MS) to the same reaction system the selective formation of monoalkylated amines occurred in high yields (Scheme 2).

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Scheme 1. Cobalt Complexes Studied for Catalytic N-Alkylation



Scheme 2. Comparison of Distinct Product Selectivities in Cobalt-Catalyzed C–N Bond Formation

Previous work:



Therefore, we present herein the versatile cobalt complex catalyzed direct N-alkylation of various amines with alcohols, highlighting the importance of homogeneous earth abundant cobalt catalysts in C–N bond coupling reactions that involve a hydrogen-borrowing mechanism.

Several related cobalt complexes (1-6, Scheme 1) previously reported were first screened for the reaction between benzyl alcohol and aniline (1.2 equiv) in toluene at reflux in a 100 mL Schlenk tube with added 4 Å MS, and the results are summarized in Table 1. It was quite delightful to observe that when 2 (2 mol % based on alcohol, generated in situ by the reaction of 1 and  $H[BAr_{4}] \cdot (Et_{2}O)_{2}$ ) was used as a catalyst, the desired Nalkylated amine 9a was detected in 98% GC yield and the imine byproduct was largely suppressed to only a trace amount, while neutral complex 1 did not favor the formation of 9a (entries 2 and 3, Table 1). However, in the latter case, the formation of an imine product in 12% yield was confirmed by GC analysis. In contrast, a control experiment in the presence of 4 Å MS, without the addition of a cobalt catalyst, gave no reaction at all (entry 1). In addition, changing the substituent (phenyl group vs cyclohexyl group) on the phosphorus atom of the PNP ligand (3) or the counteranion (4,  $BPh_4^-$  instead of  $BAr_4^{F_4}$ ) resulted in lower yields of 9a (entries 4 and 5), and adding a methyl group on the nitrogen atom of the ligand (5) also affected the reactivity (entry 6). Interestingly, the cobalt(III) complex  $6^{16}$  was found to be an active catalyst as well, displaying comparable catalytic 

 Table 1. Screening of Reaction Conditions for the Selective N 

 Alkylation of Aniline by Benzyl Alcohol<sup>a</sup>

| ОН              | + NH2    | Co catalyst (2 mol %)<br>solvent, reflux | HN - Sa                             |
|-----------------|----------|--|-------------------------------------|
| entry           | catalyst | solvent                                  | yield <sup><math>b</math></sup> (%) |
| 1               | no       | toluene                                  | 0                                   |
| $2^{c}$         | 1        | toluene                                  | 0                                   |
| 3               | 2        | toluene                                  | 98                                  |
| 4               | 3        | toluene                                  | 55                                  |
| 5               | 4        | toluene                                  | 85                                  |
| 6               | 5        | toluene                                  | 81                                  |
| 7               | 6        | toluene                                  | 97                                  |
| 8               | 7        | toluene                                  | 2                                   |
| 9               | 8        | toluene                                  | 4                                   |
| 10              | 2        | THF                                      | 45                                  |
| 11              | 2        | 1,4-dioxane                              | 66                                  |
| 12              | 2        | fluorobenzene                            | 51                                  |
| 13 <sup>d</sup> | 2        | toluene                                  | 49                                  |
| 14 <sup>e</sup> | 2        | toluene                                  | 45                                  |
| 15 <sup>f</sup> | 2        | toluene                                  | 78                                  |
|                 |          |  |                                     |

<sup>*a*</sup>Conditions: benzyl alcohol (0.5 mmol), aniline (0.6 mmol), cobalt catalyst (2 mol %), 4 Å MS (0.5 g), and solvent (4 mL) refluxed in a 100 mL Schlenk tube, 48 h. <sup>*b*</sup>Determined by GC with hexamethylbenzene as internal standard. <sup>*c*</sup>12% imine was observed. <sup>*d*</sup>Reaction run at 80 °C. <sup>*c*</sup>Reaction run in a 50 mL Schlenk tube. <sup>*f*</sup>1 mol % of **2** was used.

efficacy to the cobalt(II) catalyst 2 (entry 7). Two new cobalt(II) dihalide complexes (7 and 8, see the SI) were also examined under the same conditions, yet no significant catalytic activity was detected (entries 8 and 9). Other solvents including THF, 1,4dioxane, and fluorobenzene were tested using 2 (2 mol %) as a catalyst, but only inferior results were obtained (entries 10-12). Furthermore, lowering the reaction temperature drastically decreased the yield of 9a, and reducing the volume of the reaction vial to 50 mL also suppressed the formation of the product (entries 13 and 14). Finally, it was found that the use of only 1 mol % of 2 also afforded the desired product in 78% GC yield (entry 15). Remarkably, no basic additives were required for the highly selective formation by using the active catalyst 2, in sharp contrast to the previously reported Co(PN<sub>5</sub>P) precatalyst, where the presence of an excess amount of strong base, potassium tert-butoxide, was necessary for good catalytic performance.<sup>14</sup>

Having established the optimal catalytic conditions for the effective N-alkylation of aniline with benzyl alcohol, we sought to apply this methodology to other substrates, i.e., various alcohols and amines. First, we tested the reactions of benzyl alcohol with various aniline derivatives under standard reaction conditions (2 mol % of 2 and 4 Å MS in toluene at reflux), and the products were isolated by silica gel column chromatography after workup. The results are listed in Table 2. It was observed that electrondonating substituents such as isopropyl and methoxy groups in the ortho- or para-position of aniline favored the formation of secamine products, and 9b-d were isolated in excellent yields (entries 2–4, Table 2). In contrast, para-substituents on aniline with electron-withdrawing groups led to slightly lower yields, and in the case of 4-fluoroaniline, 4% imine as a byproduct was observed on the basis of GC analysis (entry 5, Table 2). Next, we investigated the reactions of substituted benzylic alcohols with

Table 2. Substrate Scope of the N-Alkylation Reactions of Different Amines by Alcohols<sup>a</sup>

| R <sub>1</sub>  | $\sim_{OH}$ + $R_2$ – $NH_2$  | 2 (2 mol %)<br>toluene, reflux<br>4 Å MS | $R_1 \xrightarrow{N-R_2}_{9a-r}$    |
|-----------------|-------------------------------|--|-------------------------------------|
| entry           | alcohol $(R_1 =)$             | amine $(R_2 =)$                          | yield <sup><math>b</math></sup> (%) |
| 1               | C <sub>6</sub> H <sub>5</sub> | C <sub>6</sub> H <sub>5</sub>            | 94 ( <b>9</b> a)                    |
| 2               | C <sub>6</sub> H <sub>5</sub> | $4 - Pr(C_6H_4)$                         | 90 ( <b>9b</b> )                    |
| 3               | C <sub>6</sub> H <sub>5</sub> | $4-MeO(C_6H_4)$                          | 96 ( <b>9</b> c)                    |
| 4               | C <sub>6</sub> H <sub>5</sub> | $2 - MeO(C_6H_4)$                        | 95 ( <b>9d</b> )                    |
| 5               | C <sub>6</sub> H <sub>5</sub> | $4 - F(C_6 H_4)$                         | 82 (9e), 4% imine                   |
| 6               | C <sub>6</sub> H <sub>5</sub> | $4-Cl(C_6H_4)$                           | 80 (9f)                             |
| 7               | $4-Me(C_6H_4)$                | C <sub>6</sub> H <sub>5</sub>            | 84 ( <b>9g</b> ), 13% imine         |
| 8               | $4-MeO(C_6H_4)$               | C <sub>6</sub> H <sub>5</sub>            | 90 (9h)                             |
| 9               | $4 - F(C_6 H_4)$              | C <sub>6</sub> H <sub>5</sub>            | 80 (9i), 15% imine                  |
| 10              | $(C_6H_4)CH_2$                | C <sub>6</sub> H <sub>5</sub>            | 74 (9j), 14% imine                  |
| 11              | propyl                        | C <sub>6</sub> H <sub>5</sub>            | 91 ( <b>9k</b> )                    |
| 12              | isopropyl                     | C <sub>6</sub> H <sub>5</sub>            | 96 ( <b>9l</b> )                    |
| 13              | pentyl                        | C <sub>6</sub> H <sub>5</sub>            | 90 ( <b>9m</b> )                    |
| 14              | heptyl                        | C <sub>6</sub> H <sub>5</sub>            | 95 ( <b>9</b> n)                    |
| 15              | C <sub>6</sub> H <sub>5</sub> | $(CH_2)_2C_6H_5$                         | 82 (90), 11% imine                  |
| 16              | C <sub>6</sub> H <sub>5</sub> | 2-butyl                                  | 93 (9p), 2% imine                   |
| 17 <sup>c</sup> | pentyl                        | 4-fluorobenzyl                           | 75 ( <b>9q</b> )                    |
| 18 <sup>c</sup> | heptyl                        | 1-hexyl                                  | 86 ( <b>9r</b> ), 6% imine          |
|                 |                               |  |                                     |

<sup>a</sup>Conditions: alcohol (0.5 mmol), amine (0.6 mmol), cobalt catalyst 2 (2 mol %), 4 Å MS (0.5 g), and toluene (4 mL) at reflux in a 100 mL Schlenk tube, 48 h. <sup>b</sup>Isolated yields. <sup>c</sup>Yields determined by GC analysis.

aniline. It was noticed that strongly electron-donating 4methoxy-derived benzylic alcohol was an excellent substrate for the reaction, affording the corresponding product 9h in 90% yield (entry 8, Table 2), while electron-withdrawing substituents on the benzylic alcohol slightly decreased the yield of the desired sec-amine products, yet concomitant with the observation of 15% imine byproduct (entry 9). 2-Phenylethanol was also a suitable substrate, giving the desired sec-amine 9j in reasonable yield, although a minor imine product was also detected (entry 10). Interestingly, several aliphatic alcohols also underwent the Nalkylation reactions with aniline smoothly, affording the desired products in high yields (entries 11-14). In addition, aliphatic amines were found to be suitable substrates for N-alkylation with alcohols including benzylic alcohol and aliphatic alcohols (entries 15-18). For instance, both 2-phenylethylamine and sec-butylamine reacted effectively with benzyl alcohol to provide the corresponding products in 82% and 93% yield, respectively, although minor imine byproducts were also present in the resulting reaction mixtures. Moreover, direct N-alkylation occurred between aliphatic alcohols and 4-fluorobenzylamine or 1-hexylamine producing, in the latter case, a sec-amine with a long alkyl chain in good yield. The good substrate scope involving aliphatic amines observed here is remarkable as, to the best of our knowledge, such substrates were only previously employed in an iron complex catalyzed N-alkylation through the hydrogen-borrowing process.<sup>13</sup>

Encouraged by the above findings on a wide substrate scope for the alkylation of amines by alcohols, we performed additional experiments to further assess the ability of cobalt catalyst 2 to promote the reactions of other types of substrates. First, it was noted that *m*-diaminobenzene (0.5 mmol) could also be alkylated with benzyl alcohol (2.0 equiv), and the bis-alkylation product 9s was isolated in 87% yield under standard conditions

(Scheme 3). Second, when cyclohexanol, a secondary alcohol that was not previously utilized in the N-alkylation reaction, was

### Scheme 3. N-Alkylation of 1,3-Diaminobenzene with Benzyl Alcohol



used to react with aniline under the optimal conditions, a mixture of amine, imine and ketone was detected after 48 h, with the expected N-cyclohexylaniline being the major product (48% GC yield, Scheme 4). Despite modest selectivity and yield, this result



48%

18%

2%

further indicates the exceptional catalytic activity of the Co<sup>II</sup> complex 2, which certainly deserves further investigation in the future. Finally, tert-butanol and phenol were tested for the reactions with aniline and, as expected, no coupling reactions were detected, which is consistent with a pathway involving initial alcohol dehydrogenation and supports the hydrogenborrowing mechanism for the current cobalt-catalyzed Nalkylation reaction (Scheme 5).

Scheme 5. Reactivity Test of tert-Butyl Alcohol or Phenol with Aniline



In summary, we have here reported on the selective, direct Nalkylation of both aromatic and aliphatic amines by alcohols catalyzed by a base metal cobalt complex under base-free conditions. The cobalt complex proved to be versatile for both dehydrogenation and hydrogen-transfer reactions by slightly changing the reaction conditions (adding molecular sieves). Our efficient cobalt-catalyzed (2 mol % catalyst loading) N-alkylation can be applied to a wide range of substrates, including even secondary alcohols and aliphatic amines that were scarcely addressed previously. This represents a new breakthrough in cobalt-based catalysis in relation to sustainable chemical synthesis and has implications for future catalyst design based upon earth-abundant elements.

### ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03461.

Experimental procedures and product characterization data (PDF)

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#### Notes

The authors declare no competing financial interest.

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